UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/667,569	09/21/2000	R. Rogers Yocum	BGI-141CP	8755

959 7590 10/09/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/667,569	YOCUM ET AL.	
	Examin r	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7,12,14-34,36,37,39-44,46-51 and 111-116* is/are pending in the application.

4a) Of the above claim(s) *14-18,20-23,25,29-32,36,37,39-44,46-48 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,12,19,24,26-28,33,34,49,51 and 111-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *07312003* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 1-2, 7, 12, 14-34, 36-37, 39-44, 46-51, and 111-116 are pending in the application.

[2] Applicant's amendment to the claims filed August 07, 2003, is acknowledged. This amendment replaces all previous versions and listings of the claims in the instant application.

[3] Claims 14-18, 20-23, 25, 29-32, 36, 37, 39-44, 46-48, and 50 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim.

[4] Claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, 51 and 111-116 are being examined on the merits and have been examined ONLY to the extent the claims read on the elected species.

[5] Applicant's arguments filed August 07, 2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[7] Receipt of an Information Disclosure Statement filed July 31, 2003, is acknowledged. The references cited in the IDS have been considered by the examiner and a copy of the IDS is included with the instant Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] Claims 111-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 111 (claim 116 dependent therefrom) and 112 (claims 113-116 dependent therefrom) are confusing in the recitation of "a *panE* gene with 95% or greater amino acid identity to SEQ ID NO:30" and "*panBCD* operon with 95% or greater amino acid identity to SEQ ID NO:24, 26, and 28". It is noted that genes are composed of nucleotides and not amino acids and therefore a *panE* gene would not share amino acid sequence identity with SEQ ID NO:30, which is an amino acid sequence. It is suggested that applicant clarify the claims by, for example, replacing the term "a *panE* gene with 95% or greater amino acid identity to SEQ ID NO:30" with "a *panE* gene encoding a ketopantoate reductase with 95% or greater amino acid identity to SEQ ID NO:30" and replacing the term "*panBCD* operon with 95% or greater amino acid identity to SEQ ID NO:24, 26, and 28" with "*panBCD* operon encoding ketopantoate hydroxymethyltransferase, pantothenate synthase, and aspartate 1-decarboxylase with 95% or greater amino acid identity to SEQ ID NO:24, 26, and 28, respectively". For purposes of examination, the claims have been examined accordingly.

[9] The rejection of claims 1 (claim 2 dependent therefrom), 7 (claim 12 dependent therefrom), and 51 as being unclear in the recitation of "panto-compound" is maintained for the reasons of record as set forth in the Office action mailed March 11, 2003 and for the reasons stated below. It is noted that, while the instant claims were not included in item 10 of the Office action mailed March 11, 2003, the claims were rejected in item 10a. Therefore, it is clear that claims 1, 2, 7, 12, and 51 were intended as being included in item 10 of the Office action. Applicant argues (beginning at page 10 of the amendment filed August 07, 2003) the specification provides a definition of the term "panto-compound" and provides examples of compounds encompassed by the term "panto-compound". Applicant argues that the term "panto-compound", when read in light of the specification by a skilled artisan, is particular and clear. Applicant's argument is not found persuasive.

The "definition" as provided in the specification ("pantothenate and other key compounds of the pantothenate biosynthetic pathway") is vague as to what compounds applicant considers to be encompassed by the term "panto-compound" and the examples as provided in the specification, while defining what <u>is</u> considered by applicant to be a "panto-compound", provide no indication as to what <u>is not</u> considered a "panto-compound" and thus, the scope of panto-compounds as interpreted by one of skill in the art is unclear.

[10] In order to clarify the record, it is noted that applicant states the examiner's interpretation of "panE1" and "panE" as referring to a nucleic acid encoding a polypeptide having ketopantoate reductase enzymatic activity and the examiner's

interpretation of "coaX" as referring to a nucleic acid encoding a polypeptide having pantothenate kinase enzymatic activity are correct. It is noted that applicant further states, "[m]oreover, 'coaX' is a "nucleic acid encoding a polypeptide distinct from coaA". However, the examiner can find no support for such a definition in the specification and applicant provides no support for this limiting definition in the specification. Thus, the examiner has interpreted the term "*coaX*" as any nucleic acid encoding a polypeptide having pantothenate kinase activity as stated above.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The written description rejection of claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, 51, and 115 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item 11 of the Office action mailed March 11, 2003 and the reasons stated below. It is noted that applicant's arguments do not address the written description and enablement rejections individually. Applicant's arguments (pages 12-15 of the amendment filed August 07, 2003), to the extent said arguments are directed ONLY to the written description rejection, are addressed as follows. Newly added claim 115 is drawn to a method for producing a panto-compound of claim 114, using a genus of recombinant microorganisms modified to deregulate the *B. subtilis ilvD* gene. Applicant argues that the specification is replete with teachings disclosing methods of generating microorganisms to overexpress ketopantoate reductase by, e.g., introduction of exogenous genes or modification of regulatory sequences of endogenous genes. Applicant argues the isolation of orthologous genes from divergent organisms and

production of modified organisms is so routine that multiple sources with standard techniques and kits and expression vectors are available. Applicant's arguments are not found persuasive.

As previously stated, the single disclosed species of microorganism overexpressing a *Bacillus* or *Bacillus subtilis* pantothenate biosynthetic enzyme, or a microorganism overexpressing a *panE* gene, i.e., a microorganism transformed with an expression vector comprising the nucleic acid of SEQ ID NO:29 (encoding the ketopantoate reductase of SEQ ID NO:30) fails to be representative of the entire genus of recited microorganisms. For claims reciting a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, there is substantial variation in the characteristics (e.g., structural, physiological, and functional variation) of the recited genus of microorganisms overexpressing a *Bacillus* or *Bacillus subtilis*

pantothenate biosynthetic enzyme. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of microorganisms encompasses species that are widely variant in their characteristics. As such, the disclosure of the single representative species as described above is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus. Given the lack of description of a representative number of microorganisms, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

It is noted applicant argues that, by further experimentation, "ketopantoate reductase overexpressing microorganisms can be generated" (page 13, middle of the amendment of August 07, 2003). However, such an invitation for further experimentation does not demonstrate possession of the claimed invention as required to satisfy the written description requirement of 35 USC 112, first paragraph. The written description requirement is not satisfied if one of ordinary skill in the art must first make the patented invention before he can ascertain the claimed features of that invention. See *University of Rochester v. G.D. Searle & Co. Inc.,* W.D. N.Y., No. 00-CV-6161L, 3/5/03.

[12] The scope of enablement rejection of claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, 51, and 115 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item 12 of the Office action mailed March 11, 2003 and the reasons stated below. It is noted that applicant's arguments do not address the written description and enablement rejections individually. Applicant's arguments (pages 12-15 of the amendment filed August 07, 2003), to the extent said arguments are directed ONLY to the scope of enablement rejection, are addressed as follows. Applicant argues that the specification is replete with teachings disclosing methods of generating microorganisms to overexpress ketopantoate reductase by, e.g., introduction of exogenous genes or modification of regulatory sequences of endogenous genes. Applicant argues the isolation of orthologous genes from divergent organisms and production of modified organisms is so routine that multiple sources with standard techniques and kits and expression vectors are available. Applicant argues the examiner's citation of Baigori et al. in demonstrating the unpredictability in making the recited scope of microorganisms is not relevant to the instant rejection since the claims are directed to methods of overexpressing a gene to produce pantothenate and not mutagenesis that results in mutations in unrelated genes. Applicant argues the one skilled in the art can overcome an unexpected decrease in the production of a compound by choosing a different expression method, vector, or host strain. Applicant argues it is routine in the art to screen hundreds to thousands of organisms to identify the novel strain with the desired phenotype. Applicant's arguments are not found persuasive.

The examiner reiterates his statements addressing each of the Factors of *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) as detailed at pages 8-11 of the Office action mailed March 11, 2003. As previously stated, the specification lacks the necessary guidance for making the entire scope of recited microorganisms (see pages 9 and 10 of the Office action mailed March 11, 2003) such that a high degree of unpredictability would be present in making the entire scope of recited microorganisms (see pages 10 and 11 of the Office action mailed March 11, 2003) and an undue amount of experimentation for a skilled artisan to make the entire scope of recited microorganisms used in the claimed methods. It should be noted that some of the claims provide no limitation as to which pantothenate biosynthetic enzyme(s) is/are overexpressed and all of the claims (with the exception of claim 115) provide no limitation on the structure(s) of the pantothenate biosynthetic enzyme overexpressed or the method by which the microorganism achieves overexpression. One of skill in the art would recognize that, based on the lack of guidance, e.g., guidance regarding structures of other *Bacillus* or *Bacillus subtilis* pantothenate biosynthetic enzymes or ketopantoate reductase (from any organism) such that *all* encoding nucleic acids for the enzymes encompassed by the scope of the claims can be isolated by those methods considered "routine" by applicant and used for overexpression, the high degree of unpredictability as supported by the prior art, and the enormous amount of experimentation necessary to make the entire scope of claimed methods, the disclosure fails to provide the necessary teachings for enablement under 35 USC 112, first paragraph.

It is further noted that in view of applicant's arguments it is clear that further experimentation is required to in order that the specification enables a skilled artisan to practice the entire scope of claimed methods. Such guidance provided by the specification therefore merely provides a starting point or a direction for further research that, at most, will enable a skilled artisan to attempt to discover how to *practice* the entire scope of the claimed invention. However, such teachings do not amount to an enabling disclosure. See *University of Rochester v. G.D. Searle & Co. Inc.,* W.D. N.Y., No. 00-CV-6161L, 3/5/03.

Claim Rejections - 35 USC § 102

[13] The rejection of claims 1, 2, 7, 19, 24, 26, 27, 33, and 34 under 35 U.S.C. 102(b) as being anticipated by Baigori et al. (*J Bacteriol* 173:4240-4242) is maintained for the reasons of record as set forth in item 13 at pages 12-13 of the Office action mailed March 11, 2003 and for the reasons stated below. Applicant argues (beginning at the middle of page 15 of the amendment filed August 07, 2003) Baigori et al. teach *Bacillus subtilis* mutants that are blocked in the synthesis of pantothenic acid, i.e., pantothenate auxotrophs. For clarity, the examiner notes these strains are identified as UR1 and UR2. Applicant argues Baigori et al. teach that revertants of strains UR1 and UR2 show normal levels of transferase and reductase activity and nothing is discussed in the reference of overexpression, which would lead to higher levels of transferase and reductase activities. Applicant argues that the increased level of transferase and reductase activities of revertant strains UR3 and UR4 relative to strains UR1 and UR2

(as shown at page 4242 in Table 2) are not associated with transformants of UR1 and UR2, but rather are associated with revertants of strains UR1 and UR2 such that UR1 and UR2 have spontaneously reverted to their original or wild-type phenotype. Applicant argues nothing is disclosed in the reference about a method for the production of pantothenate by overexpressing or recombining genes of the pantothenate biosynthesis chain. Applicant argues the claimed invention is opposite to the teachings of Baigori et al. and the reference is not relevant in view of novelty and obviousness. Applicant's argument is not found persuasive.

In order to clarify the record, it is noted that strain UR3 has not been generated by transformation of DNA from *Bacillus* strain BD170 as stated by the examiner at page 13, lines 9-10 of the Office action mailed March 11, 2003. However, Baigori et al. nonetheless anticipate the claimed invention. As stated above, Baigori et al. teach *Bacillus subtilis* strains UR1 and UR2, which are severely deficient in ketopantoate hydroxymethyltransferase and ketopantoic acid reductase activities, respectively (page 4240, right column, top and page 4241, Table 2). Baigori et al. teach, "*pan*+ transformants of strains UR1 and UR2 (the DNA was obtained from strain BD170) also showed normal levels of transferase and reductase activity" (page 4240, right column, middle). Thus, transformation of UR1 and UR2 with DNA from strain BD170 resulted in overexpression of transferase and reductase activities relative to strains UR1 and UR2. As such, Baigori et al. anticipate the claimed invention and the reference is directly relevant to the instant rejection and claimed invention.

Applicant further argues (beginning at the middle of page 16 of the amendment of August 07, 2003) the methodology described in Baigori et al. for producing *panE* mutants would not result in the successful production of such mutants for the following reasons: the classification of the *panB* and *panE* mutants was based on reduction in transferase and reductase activities, the mutations were claimed to be mapped to the *purE-tre* region of the *Bacillis* chromosome and the mutations are described as being close together, and the *panE* gene was isolated to the 60° region of the genome, when in fact the gene is located at 135° (it is noted that applicant provides no supporting evidence of the location of the *panE* gene in the *Bacillus* chromosome). Applicant's argument is not found persuasive.

As supported by applicant, the meaning of the term "*panE*" in the claims is a nucleic acid encoding a polypeptide having ketopantoate reductase enzymatic activity (see page 11, bottom of the amendment filed August 07, 2003). There is no structural limitation provided for the nucleic acid encoding *panE* as recited in the claims and the transformation of strain UR2 (exhibiting significantly reduced reductase activity) with DNA from strain BD170 restored reductase activity as described above. Therefore, the DNA from strain BD170 (regardless of the classification of the *panE* mutation or chromosomal location of the DNA from strain BD170) clearly comprises a nucleic acid that encodes a polypeptide having ketopantoate reductase activity and would satisfy the meaning of the term "*panE*" as stated above.

Applicant additionally argues (beginning at the bottom of page 16 of the amendment of August 07, 2003) even if one were to assume for the sake or argument

that Baigori et al. had described such a microorganism, the reference would fall short of teaching methods of producing panto-compounds comprising culturing a microorganism that expresses ketopantoate reductase AND a second pantothenate biosynthetic enzyme. Applicant argues that even if the reference teaches a retransformed *panE* mutant having normal ketopantoate reductase activity, this microorganism would fail to produce the recited level of panto-compound as recited in claims 14-20, 23, and 25-27. Applicant's argument is not found persuasive. It is noted that the DNA from strain BD170 used to transform UR1 and UR2 contains a nucleic acid encoding a polypeptide having ketopantoate reductase activity AND ketopantoate hydroxymethyltransferase activity as the DNA restored both activities. Thus, the microorganism overexpresses ketopantoate reductase AND ketopantoate hydroxymethyltransferase relative to UR1 and UR2. Applicant's argument addressing the "at least 0.2g/L panto-compound" limitation allegedly present in claims 14-20, 23, and 25-27 is acknowledged. However, the examiner can find no such limitation in the claims filed in the amendment of August 07, 2003. Even if such limitation were present, it is noted that claims 14-18, 20, 23, and 25 remain withdrawn from consideration.

[14] The rejection of claims 7, 19, 24, and 26 under 35 U.S.C. 102(b) as being anticipated by Frodyma et al. (*J Biol Chem* 273:5572-5576) is maintained for the reasons of record as set forth in item 14 at pages 13-14 of the Office action mailed March 11, 2003 and for the reasons stated below. Applicant argues (beginning at the middle of page 17 of the amendment filed August 07, 2003) Frodyma et al. do not teach

a method for producing a panto-compound by overexpressing a *Bacillus* pantothenate biosynthetic enzyme as recited in claim 1 or disclose a method of producing pantothenate according to claim 14. Applicant argues Frodyma et al. do not teach overexpressing a second pantothenate biosynthetic enzyme in addition to the *apba* gene product. Applicant's argument is not found persuasive.

It is noted that the rejection is not directed to claims 1 or 14 as argued by applicant. Furthermore, it is noted that claim 14 remains withdrawn from consideration. Also, none of the rejected claims requires the limitation of overexpression of a second pantothenate biosynthetic enzyme.

Applicant further argues that Frodyma et al. do disclose the limitation of claim 19, which requires a beta-alanine independent high yield production method for pantothenate. Applicant's argument is not found persuasive.

The culture conditions for the growth of the transformants of Frodyma et al. do not require the addition of beta-alanine, and thus the growth of the transformants is independent of beta-alanine.

Claim Rejections - 35 USC § 103

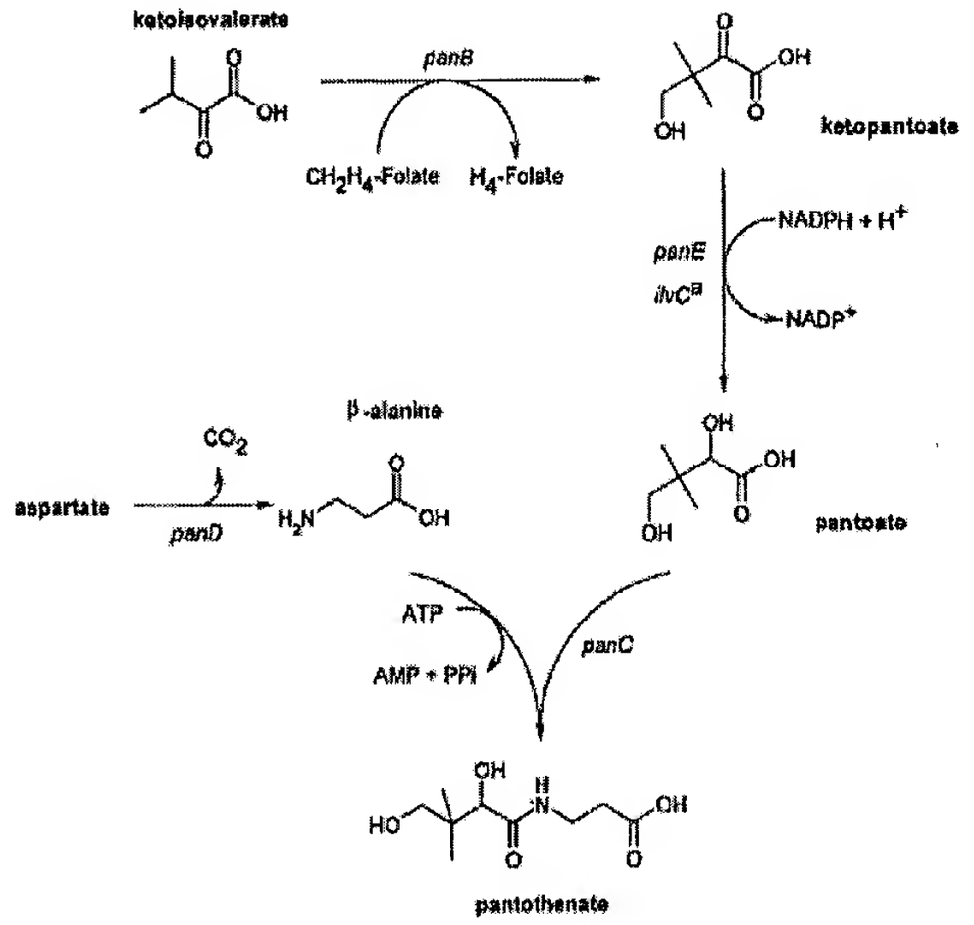
[15] The rejection of claim 12 under 35 U.S.C. 103(a) as being unpatentable over Frodyma et al. (supra) in view of Hikichi et al. (US Patent 5,518,906) is maintained for the reasons of record as set forth in item 15 at pages 14-15 of the Office action mailed March 11, 2003 and for the reasons stated below. Applicant argues (beginning at the top of page 18 of the amendment filed August 07, 2003) that Hikichi et al. do not teach

production of panto-compounds by overexpression of ketopantoate reductase (*panE*) and at least one other pantothenate biosynthetic enzyme or about microbes possessing a resistance against salicylic acid and Frodyma et al. do not disclose overexpression of *panE* for the production of pantothenic acid and thus the invention is not obvious. Applicant argues that to combine the two references is only obvious once the methods of the present invention are known. Applicant's argument is not found persuasive.

The examiner is unclear as to applicant's argument addressing Hikichi et al. and the alleged failure to disclose anything about "microbes possessing a resistance against salicylic acid". In fact, applicant acknowledges that Hikichi et al. disclose such teachings (see page 18, second paragraph of the amendment filed August 07, 2003). The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In the instant case, while Hikichi et al. does not teach overexpression of ketopantoate reductase (*panE*) for panto-compound production and Frodyma et al. do not disclose overexpression of *panE* for the production of pantothenic acid, there is clear motivation to combine the cited references as Hikichi et al. teach that a strain transformed with a plasmid carrying genes involved in the biosynthesis of pantothenate accumulates increased levels of pantothenate in the culture medium and Frodyma et al. teaches a gene involved in the biosynthesis of pantothenate. Therefore, one of ordinary skill in the art would have a clear motivation to overexpress the gene of Frodyma et al. in addition

to the genes of Hikichi et al. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made – as is the instant case as evidenced by the publication and/or filing dates of the references, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

Applicant argues (beginning at the top of page 19) in order to create an obviousness rejection three requirements must be met – 1) motivation to combine the references; 2) the references must teach all claim limitations; and 3) the references must teach all limitations. Applicant argues there is no motivation to combine the cited references. Applicant argues Hikichi et al. teaches overexpression of the *panBCD* operon, but is silent in regards to overexpression of other pantothenate biosynthetic enzymes and Frodyma et al. teaches overexpression of *panE* but fails to teach or suggest overexpressing *panE* in combination with a second pantothenate biosynthetic enzyme. Applicant argues it is improper to reconstruct the invention from the prior art using the claims as a blueprint and that there must be some reason to combine the references other than hindsight itself. Applicant's argument is not found persuasive.



As stated and reiterated here in the Office action mailed March 11, 2003, the cited references teach all limitations of the claims, provide a motivation for combining the cited references and provide a reasonable expectation of success for practicing the claimed invention (see item 15, pages 14-15 of the Office action). One of ordinary skill in the art, knowing that ketopantoate reductase is an enzyme of the pantothenate biosynthetic pathway as shown in Figure 1 (page 5573) of Frodyma et al. and copied above, would have wanted to co-overexpress the *panE* gene of Frodyma et al. with the *panB, panC,* and *panD* genes of Hikichi et al., particularly as *panE* is directly involved in the biosynthetic conversion of ketoisovalerate to pantothenate. Hikichi et al. teach "the inventors investigated application of gene recombination technology to strain breeding, finding that a strain transformed with a plasmid carrying genes involved in biosynthesis of pantothenic acid or a salt thereof accumulates D-pantothenic acid… …at even higher concentrations in the medium" (column 2, lines 33-38). Therefore, as the product of the *panE* gene is a involved in the biosynthesis of pantothenic acid as evidenced by Figure 1 of Frodyma et al. (reprinted above), one clearly would have wanted to co-express the *panE* gene of Frodyma et al. with the *panB, panC,*and *panD* genes of Hikichi et al. Regarding applicant's argument that it is improper to reconstruct the invention from the

prior art using the claims as a blueprint, as previously stated, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In this case, the teachings of the cited references take into account only knowledge which was available at the time of the invention and therefore, the rejection is proper.

[16] The rejection of claims 49 and 51 under 35 U.S.C. 103(a) as being unpatentable over Baigori et al. (*supra*) or Frodyma et al. (*supra*) in view of Hikichi et al. (*supra*) as applied to claim 12 above, and further in view of Vallari et al. (*J Bacteriol* 170:3961-3966) and Leung (Coenzyme-A Technologies Inc., Technical Articles and Scientific Research, "Coenzyme-A 'The Master Coenzyme'") is maintained for the reasons of record as set forth in item 16 at pages 15-17 of the Office action mailed March 11, 2003 and for the reasons stated below. It should be noted that, due to an editing error during drafting of the Office action mailed March 11, 2003, the reference of Baigori et al. (*supra*) was inadvertently included in the instant rejection. However, it is clear based on the body of the text that this reference was unintentionally included. Applicant addresses the Leung reference by arguing (beginning at the top of page 21 of the amendment filed August 07, 2003) that the teachings of Leung are "immaterial to the present specification". Applicant addresses the reference of Vallari et al. by arguing the teachings of Vallari et al. do not target by mutation any of the genes necessary for

panto-compound production and assert that the instant invention describes the specific isolation of the *coaX* gene. Applicant argues that if Vallari et al. believe that pantothenate kinase is the most important determinant in the CoA biosynthetic rate, there would be no motivation to improve that production and to combine the references of Frodyma et al. and Hikichi et al. Applicant's arguments are not found persuasive.

As stated in a previous Office action, the term "*coaX*" has been interpreted according to MPEP 2111 as meaning any nucleic acid encoding a pantothenate kinase, particularly as applicant has provided no limitations on the characteristics of a *coaX* gene that would distinguish the "*coaX*" gene of claim 39 from the gene of Vallari et al., and the examiner has interpreted the term accordingly. See also item 10 of the instant Office action. Even assuming *arguendo* that the term "*coaX*" is defined sufficiently in the specification such that the gene of Vallari et al. would not meet this definition, it is noted that claim 41 is not limited to a *coaX* gene. Baigori et al. present Figure 1 (page 4241) showing the biosynthesis of coenzyme A (reprinted herein).

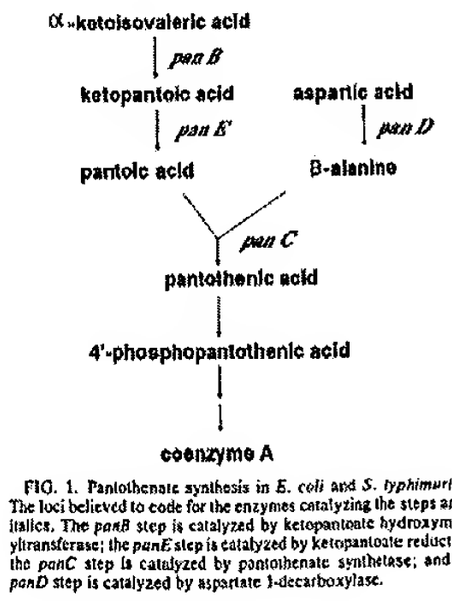


FIG. 1. Pantothenate synthesis in *E. coli* and *S. typhimurium*. The loci believed to code for the enzymes catalyzing the steps are in italics. The *panB* step is catalyzed by ketopantoate hydroxymethyltransferase; the *panE* step is catalyzed by ketopantoate reductase; the *panC* step is catalyzed by pantothenate synthetase; and the *panD* step is catalyzed by aspartate 1-decarboxylase.

The gene products of *panB, panC,* and *panD* as taught by Hikichi et al., the gene product of *panE* as taught by Frodyma et al., and pantothenate kinase, which catalyzes the conversion of pantothenic acid to 4'phosphopantothenic acid, are required for biosynthesis of CoA. At the time of the invention, one of ordinary skill in the art would have recognized that increasing production of the intermediates involved in the biosynthesis of CoA would have resulted in an increased production of CoA.

Furthermore, Vallari et al. teach a pantothenate kinase that is deregulated to feedback inhibition as depicted in Figure 6 (page 3965) and reprinted herein. Therefore, contrary to applicant's arugment, one of ordinary skill in the art would have wanted to increase the production of intermediates of CoA biosynthesis by co-expression the *panB, panC,* and *panD* genes of Hikichi et al. and/or expression of the *panE* gene of Frodyma et al. in the host exhibiting a feedback deregulated pantothenate kinase of Vallari et al. One of ordinary skill in the art would recognize that Increasing the levels of precursors of CoA by expressing the genes of Hikichi et al. and/or Frodyma et al. would have led to an increased rate of CoA production as Vallari et al. teach that regulation of the pantothenate kinase reaction is the most important determinant in the rate of CoA biosynthesis (page 3961, left column). One would have clearly been motivated to increase the production of CoA as this compound is beneficial in treating acne as taught by Leung.

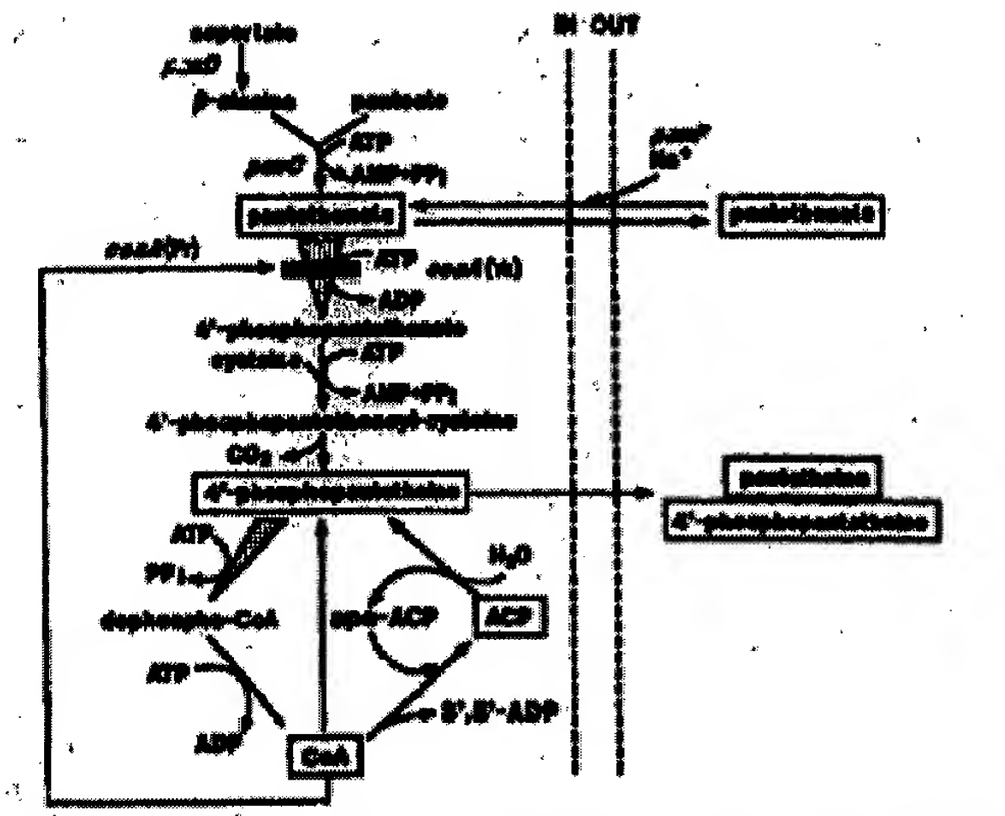


FIG. 6. Regulation of CoA content in *E. coli*. Pantothenate kinase is the principal regulatory site in CoA biosynthesis. This enzyme is the product of the *coaA* gene, and its activity is governed by feedback inhibition primarily by nonesterified CoA and secondarily by CoA thioesters. CoA inhibits pantothenate kinase catalytic activity by competing with ATP. More pantothenate is produced than is used for CoA synthesis, and the unphosphorylated pantothenate is released into the medium. Extracellular pantothenate

Conclusion

[17] Status of the claims:

- Claims 1-2, 7, 12, 14-34, 36-37, 39-44, 46-51, and 111-116 are pending.
- Claims 14-18, 20-23, 25, 29-32, 36, 37, 39-44, 46-48, and 50 remain withdrawn from further consideration.
- Claims 1, 2, 7, 12, 19, 24, 26-28, 33, 34, 49, 51, and 111-116 are rejected.
- No claim is in condition for allowance.

Applicant's amendment to claim 1 necessitated the new rejection under 35 USC 102(b). **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

REBECCA E. PRUSTY
PRIMARY EXAMINER
GROUP 1600

1600